Cancer Mortality Among Patients With Hansen's Disease[1]

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ABSTRACT—For the evaluation of cancer risks associated with immunodeficiencies experienced by patients with Hansen's disease (leprosy) and for the assessment of possible adverse effects of dapsone therapy, a follow-up study was conducted of 1,678 patients admitted to the National Hansen's Disease Center in Carville, La., between 1939 and 1977. Overall, no substantial cancer mortality was observed (standardized mortality ratio=1.3), nor was there any excess among patients exhibiting defects in cellular immunity by virtue of lepromatous forms of the disease. Notable was the absence of any significant excess of lymphoma (5 observed vs. 2.3 expected), despite the predominance of this tumor in certain other immunodeficiency states. Several cancer sites (oral, bladder, and kidney) occurred excessively, but reasons for the elevations were obscure. Although dapsone has been implicated as a carcinogen in laboratory animals, the use of sulfones, including dapsone, did not appear to affect significantly the risk of any cancers in this population.—JNCI 1984; 72:109–114.

A number of studies of patients with altered immune status have shown that they experience excess risks of cancer (*1, 2*). While the excesses have often been specific for lymphoma, the relative contributions of immunosuppression and immunostimulation have been uncertain. Most immune status-altered populations showing cancer excesses have featured both immunosuppression and immunostimulation, although in some conditions the level of cancer risk has been related to the extent of stimulation (*3*). Of interest for clarification of these issues are patients with Hansen's disease, particularly those with lepromatous forms, who experience marked defects in their cellular response to *Mycobacterium leprae* and who may have generalized depressed cellular immunity of varying severity (*4*).

Previous studies of lymphoma risk among patients with Hansen's disease (*5–9*) have failed to show any substantial excesses. However, most of the studies have been limited by small numbers of study subjects or by limited follow-up, including a previous study of patients admitted to the National Hansen's Disease Center in Carville, La., during the period 1939–63 (*8, 9*). A follow-up study of patients admitted between 1939 and 1977 offered an opportunity to expand the study cohort as well as to lengthen the follow-up. In addition, it permitted an evaluation of the effects of recently introduced therapeutic agents, including dapsone, a demonstrated carcinogen in laboratory animals (*10–14*).

METHODS

Eligible for study were all 1,818 patients admitted for treatment of histologically confirmed Hansen's disease to the National Hansen's Disease Center in Carville, La., between January 1, 1939, and December 31, 1977. Excluded from study were 140 patients whose disease lacked histologic confirmation, leaving a study cohort of 1,678 patients.

Medical records were reviewed for all study subjects, and information was abstracted on demographic characteristics, medical history, clinical evaluation, and treatment. On the basis of clinical and histologic assessments during various admissions, patients were classified as having lepromatous, tuberculoid, borderline, or indeterminate disease according to the system outlined by Ridley (*15*).

Attempts were made to determine vital status for all patients as of January 1, 1978. A substantial proportion (13.3%) of the study cohort remained at the National Hansen's Disease Center after their first admission and were resident at the time of close of the study. For the remaining 1,454 patients, follow-up was pursued through several sources. The major source of follow-up information was the last physician or health facility noted in the patient's medical record. In addition, for all patients with a social security number, names and numbers were submitted to the Social Security Administration to ascertain the occurrence of death benefit claims.

For the 552 patients found to be deceased, death certificates were requested from state vital statistics offices. A total of 527 certificates (95.6%) were successfully obtained. Certificates were unavailable for 25 patients; 10 of these patients were known to have died in foreign countries. All death certificates were coded for underlying and multiple causes of death by a trained nosologist according to the rules in effect at the time of death, with

ABBREVIATIONS USED: CI=confidence interval(s); ICD-8=Eighth Revision of the International Classification of Diseases; SMR=standardized mortality ratio(s).

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codes assigned from the ICD-8 (*16*).

For derivation of expected numbers of cancer deaths, a standard computer program (*17*) was used to accumulate person-years and to generate expected numbers. Because of the diverse ethnic background of the study population, total U.S. mortality rates were not considered appropriate. To accommodate the ethnic variation, we applied race- and age-specific U.S. mortality rates for whites, blacks, and Chinese (*17, 18*) to corresponding person-years for the non-Hispanic whites, blacks, and Asians. Chinese rates were chosen for all Asians since few of the Oriental subjects were of Japanese descent. Since appropriate time-specific mortality rates for the entire population of U.S. Hispanics are not existent and the majority of the Hispanic study subjects were of Mexican descent, we chose mortality rates for New Mexico Hispanics to generate expected values for this group. Because these rates are available only for the mid-1970's, some of the expected values for sites experiencing marked changes over time might be either overestimated (e.g., lung) or underestimated (e.g., stomach and cervix). However, the biases introduced would be less substantial than those resulting from the use of time-specific non-Hispanic rates.

The measure of association used is the ratio of observed-to-expected numbers of deaths, referred to as the SMR. The 95% CI on these ratios assumed an underlying Poisson distribution (*19*) and were considered statistically significant at the $P<.05$ level when the lower limit exceeded 1.0.

TABLE 1.—*Demographic characteristics of Hansen's disease patients admitted to the National Hansen's Disease Center between 1939 and 1977*

Demographic characteristic	No.	Percent
Sex		
Male	1,114	66.4
Female	564	33.6
Race		
White, non-Hispanic	564	33.6
White, Hispanic	709	42.3
Black	163	9.7
Asian–Pacific Islander	232	13.8
American Indian–Alaskan Native	3	0.2
Unknown	7	0.4
Age, yr, at first admission		
<20	132	7.9
20–29	363	21.6
30–39	381	22.7
40–49	299	17.8
50–59	241	14.4
60–69	174	10.4
≥70	88	5.2
Year of first admission		
<1940	173	10.3
1940–49	416	24.8
1950–59	332	19.8
1960–69	421	25.1
1970–77	336	20.0
Born in the United States		
Yes	869	51.8
No	809	48.2
U.S. citizen		
Yes	1,224	72.9
No	454	27.1

RESULTS

Characteristics of the 1,678 study subjects are shown in table 1. Most of the patients (66.4%) were male. Most were white, but a higher proportion of the total population was Hispanic (42.2%) than non-Hispanic (33.6%). In addition, 13.8% of patients were of Asian or Pacific Island descent and 9.7% were black. The mean age at first admission was 40.6 years, with a range of 6–95 years. The mean year of first admission was 1955.5 (range, 1901–77). Patients were fairly equally distributed in terms of whether they were born in the United States or not, with 51.8% having been born in the United States and 48.2% having been born elsewhere. Of those born outside the United States, 33.9% were born in Mexico, 20.0% in Puerto Rico, the U.S. Virgin Islands, or other U.S. trust territories, 8.5% in other Caribbean countries, 11.0% in the Philippines, 12.0% in other Asian countries, 6.4% in Europe, 5.9% in Central and South America, and 2.2% in other or unknown locales. At the time of last admission, 72.9% of the study population were noted to be U.S. citizens.

Table 2 shows the follow-up status of patients according to various demographic parameters, including race, place of birth, and U.S. citizenship. A total of 23,755 person-years was accrued for the study subjects. Most of the person-years were contributed by the Hispanic patients, as well as by those who were born in the United States and those who were U.S. citizens. The mean age at first admission was highest (42.8 yr) for non-Hispanic whites and lowest for nonwhites (37.2 yr). Non-Hispanic whites had an earlier mean year of entry (1953) and a longer mean follow-up (16.0 yr) than patients of other races. In addition, U.S.-born patients and U.S. citizens had an earlier mean year of entry and a longer mean follow-up duration than did foreign-born patients and non-U.S. citizens. By the close of the study, 552 patients (32.9%) were deceased, 778 (46.4%) were known to be alive, and 348 (20.7%) were lost to follow-up. The proportion deceased was highest (42.9%) for non-Hispanic whites, and the lost-to-follow-up rate was lowest (14.0%) for those born in the United States.

The SMR for males and females are shown in table 3 for all cancers combined and for individual sites. A total of 77 deaths from cancer was observed, yielding an SMR of 1.3 (95% CI, 1.0–1.6). There were significant excesses of cancers of the oral cavity (SMR=4.0), bladder (3.2), and kidney (3.2). In addition, a nonsignificant excess was seen for lymphoma (2.2).

In males the SMR was 1.5 (1.1–1.9) for all cancers, based on 60 observed deaths. There were significant excesses of cancers of the oral cavity (4.5) and bladder (4.0) and of lymphoma (3.0). In addition, a nonsignificant excess was observed for cancer of the kidney (3.1).

In females the SMR was 1.0 (0.6–1.5), resulting from 17 observed cancer deaths. There were nonsignificant elevations for cancers of several sites, including kidney cancer (3.8). Approximately twofold elevations in risk

were observed for cancers of the stomach, colon, rectum, liver, and gallbladder, with these cancers contributing 8 of the 17 deaths.

Further analysis of individual sites considered the patients' characteristics such as ethnic background and types of Hansen's disease. As shown in table 4, the cancer excess was largest for nonwhites (SMR=1.7), who had especially high risks for cancers of the oral cavity (4.0), bladder (7.4), and kidney (11.8). Among the Hispanic patients, the risk for all malignant neoplasms was not significantly increased (SMR=1.4), but there was a significant excess (3.2) of cancers of the liver and gallbladder. Among non-Hispanic white patients, the SMR was 1.1 for all cancers. The only cancer site revealing a significant excess was cancer of the oral cavity (3.8), but nonsignificant excesses of twofold or greater were seen

TABLE 2.—*Follow-up characteristics of Hansen's disease patients admitted to the National Hansen's Disease Center between 1939 and 1977*

Study subjects	No.	Person-years	Mean age, yr, at entry	Mean yr at entry	Mean yr of follow-up	No. dead (%)	Vital status	
							No. alive (%)	No. lost (%)
All study subjects	1,678	23,755.2	40.6	1955.5	14.2	552 (32.9)	778 (46.4)	348 (20.7)
Whites, non-Hispanic	564	9,029.2	42.8	1953.0	16.0	242 (42.9)	226 (40.1)	96 (17.0)
Whites, Hispanic	709	9,442.4	40.8	1958.7	13.3	195 (27.5)	367 (51.8)	147 (20.7)
Other	405	5,284.4	37.2	1957.6	13.0	115 (28.4)	185 (45.7)	105 (25.9)
U.S.-born	869	14,213.5	42.1	1954.4	16.3	349 (40.2)	398 (45.8)	122 (14.0)
Foreign-born	809	9,542.2	40.0	1958.8	11.8	203 (25.1)	380 (47.0)	226 (27.9)
U.S. citizen	1,224	19,358.1	40.8	1955.5	15.8	427 (34.9)	594 (48.5)	203 (16.6)
Noncitizen	454	4,397.5	40.1	1959.3	9.7	125 (27.5)	184 (40.5)	145 (31.9)

TABLE 3.—*SMR for cancer deaths by sex among Hansen's disease patients[a] admitted to the National Hansen's Disease Center between 1939 and 1977[b]*

ICD-8	Cancer deaths	Males (n=1,108)			Females (n=563)			Total (n=1,671)		
		O	E	O/E	O	E	O/E	O	E	O/E
140–209	All cancers	60	40.62	1.5[c]	17	17.92	0.9	77	58.54	1.3[d]
140–149	Oral	7	1.55	4.5[c]	0	0.20	—	7	1.74	4.0[c]
151	Stomach	5	4.19	1.2	2	1.23	1.6	7	5.42	1.3
153–154	Colon and rectum	3	5.30	0.6	4	2.37	1.7	7	7.68	0.9
155–156	Liver and gallbladder	3	2.11	1.4	2	1.05	1.9	5	3.17	1.6
157	Pancreas	2	2.71	0.7	1	1.00	1.0	3	3.71	0.8
160–163	Lung	13	8.88	1.5	2	1.35	1.5	15	10.24	1.5
180–184	Female genital				2	3.34	0.6	2	3.34	0.6
185	Prostate gland	2	3.91	0.5				2	3.91	0.5
188	Bladder	5	1.26	4.0[c]	0	0.31	—	5	1.57	3.2[d]
189	Kidney	3	0.96	3.1	1	0.27	3.7	4	1.23	3.3[d]
200–203 and 208	Lymphoma	5	1.64	3.0[d]	0	0.64	—	5	2.26	2.2
	Others[e]	12	8.11	1.5	3	6.16	0.5	15	14.27	1.1

[a]Seven patients were excluded due to missing information on race.
[b]O=observed; E=expected.
[c]$P<.01$.
[d]$P<.05$.
[e]"Others" include 2 deaths each from esophageal cancer, brain cancer, and leukemia; 1 death each from nasal cancer, bone cancer, malignant melanoma, and breast cancer; 2 deaths from secondary neoplasms; and 3 deaths from neoplasms of unknown primary site.

TABLE 4.—*SMR for selected cancer deaths by race among Hansen's disease patients admitted to the National Hansen's Disease Center between 1939 and 1977[a]*

ICD-8	Cancer deaths	Non-Hispanic whites (n=564)			Hispanic whites (n=709)			Other (n=398)		
		O	E	O/E	O	E	O/E	O	E	O/E
140–209	All cancers	31	27.89	1.1	25	18.00	1.4	21	12.65	1.7[b]
140–149	Oral	3	0.78	3.8[b]	1	0.22	4.5	3	0.74	4.1[b]
155–156	Liver and gallbladder	0	0.85	—	4	1.26	3.2[b]	1	1.06	0.9
188	Bladder	2	0.93	2.2	1	0.37	2.7	2	0.26	7.7[b]
189	Kidney	2	0.56	3.6	0	0.50	—	2	0.17	11.8[b]
200–203 and 208	Lymphoma	2	1.21	1.7	2	0.69	2.9	1	0.36	2.8

[a]O=observed; E=expected.
[b]$P<.05$.

for cancers of the bladder (2.2) and kidney (3.6).

SMR were calculated separately for the 1,131 patients with lepromatous disease and the 540 with other forms (tuberculoid, borderline, or indeterminate) (table 5). There was no substantial difference in the overall SMR between the lepromatous patients (1.3) and patients with nonlepromatous forms of disease (1.4). SMR for oral, bladder, and kidney cancers were elevated in both forms of the disease, although the risks were higher in the nonlepromatous patients. The slight excess of liver and gallbladder cancers was limited to the lepromatous patients, while the lymphoma excess was mainly among those with nonlepromatous disease.

To assess effects of disease duration, we examined more closely the several cancer sites with elevated risks according to the interval between initial hospital admission and death (table 6). No cancer sites showed any clear or consistent trends in risk with these intervals, although the highest value for hepatobiliary cancers was seen in the ≥20-year category (SMR=1.9).

Analysis of effects associated with exposure to sulfone preparations considered information on medications prescribed during hospitalizations. Person-years for users of dapsone and diasone (which is metabolized to dapsone after ingestion) were accumulated from time of first exposure, and cancer deaths were examined according to specific intervals since first use (table 7). Duration of sulfone use was not available; however, since the therapeutic recommendation for Hansen's disease often involves use for the remainder of a patient's life, time since first exposure was thought to be a reasonable surrogate for duration of use. No clear trends across the three "dose" categories were seen for oral, bladder, or kidney cancers. No deaths due to liver or gallbladder cancers or lymphomas were seen in the unexposed group; however, the SMR were slightly higher in the long-term versus the short-term users for both sites.

TABLE 5.—*SMR for selected cancer deaths by type of disease at initial admission among Hansen's disease patients admitted to the National Hansen's Disease Center between 1939 and 1977*[a]

ICD-8	Cancer deaths	Lepromatous (*n*=1,131)			Other (*n*=540)		
		O	E	O/E	O	E	O/E
140–209	All cancers	53	41.61	1.3	24	16.93	1.4
140–149	Oral	4	1.21	3.3[b]	3	0.53	5.7[c]
155–156	Liver and gallbladder	4	2.18	1.8	1	0.98	1.0
188	Bladder	2	1.13	1.8	3	0.44	6.8[b]
189	Kidney	2	0.90	2.2	2	0.33	6.1[b]
200–203 and 208	Lymphoma	3	1.65	1.8	2	0.61	3.3

[a]O=observed; E=expected.
[b]$P<.05$.
[c]$P<.01$.

DISCUSSION

This study revealed no substantial excess mortality from cancer among Hansen's disease patients, a finding consistent with results from earlier surveys of patients from Carville (*8, 9*), as well as from institutions in Puerto Rico (*5*), Hawaii (*6*), and Japan (*7*). We anticipated that excess cancer risks might be seen among patients with

TABLE 6.—*SMR for selected cancer deaths according to interval between initial hospital admission and death*[a]

Cancer deaths	Interval between initial hospital admission and death								
	<10 yr			10–19 yr			≥20 yr		
	O	E	O/E	O	E	O/E	O	E	O/E
Oral	2	0.67	3.0	3	0.51	5.9[b]	2	0.56	3.6
Liver and gallbladder	2	1.23	1.6	1	0.89	1.1	2	1.03	1.9
Bladder and kidney	3	1.03	2.9[b]	3	0.78	3.8[b]	3	0.99	3.0
Bladder	1	0.57	1.8	2	0.44	4.5	2	0.58	3.4
Kidney	2	0.46	4.3[b]	1	0.34	2.9	1	0.41	2.4
Lymphoma	2	0.85	2.4	3	0.62	4.8[b]	0	0.74	—

[a]O=observed; E=expected.
[b]$P<.05$.

TABLE 7.—*SMR for selected cancer deaths according to sulfone use and interval between sulfone use and death*[a]

Cancer deaths	No sulfone use[b]	Sulfone users[b]	
		<10 yr	≥10 yr
Oral	4.7 (2/0.43)	3.3 (2/0.61)	4.8[c] (3/0.63)
Liver and gallbladder	— (0/0.69)	1.7 (2/1.15)	2.6 (3/1.17)
Bladder and kidney	— (0/0.55)	5.7[d] (6/1.06)	2.7 (3/1.10)
Bladder	— (0/0.31)	5.0[c] (3/0.60)	3.2 (2/0.62)
Kidney	— (0/0.24)	6.5[d] (3/0.46)	2.1 (1/0.48)
Lymphoma	— (0/0.41)	2.4 (2/0.82)	3.3 (3/0.92)

[a]Seventy-four patients were excluded due to missing information on sulfone use.
[b]Observed/expected are shown *in parentheses*.
[c]$P<.05$.
[d]$P<.01$.

lepromatous disease, who have immunologic defects resembling those previously associated with a predisposition to cancer (*2*). However, we found no evidence of an excess risk among these patients; in fact, patients with tuberculoid and other forms of Hansen's disease were generally at a higher cancer risk for sites of interest than were patients with lepromatous disease.

There was no large excess risk for lymphoma among patients with Hansen's disease, despite clinical reports of an association (*20–22*). We did see a slightly elevated risk overall (SMR=2.2), particularly for males (SMR=3.0). However, in contrast to our original hypothesis, we saw no significant excess risk among patients with the most impaired immune function, i.e., with lepromatous disease. In other patients who exhibit both immunosuppression and immunostimulation, including renal transplant recipients (*23*) and patients with Sjögren's syndrome (*3*), excess risks of 35- to 40-fold have been reported for lymphoma. In these studies, the predominant cell type has been histiocytic lymphoma (reticulum cell sarcoma), while in our survey the reported tumors included two cases of multiple myeloma and one case each of Hodgkin's disease, lymphosarcoma, and lymphomatoid granulomatosis. If the risk of lymphoma among patients with certain other immunodeficiencies had prevailed among Hansen's disease patients, we should have observed over 100 lymphomas, as compared to the 6 that developed. It is difficult to explain the discrepant risks of lymphoma in various studies of impaired immunity, but there may be clues in the specific immunoregulatory mechanisms associated with Hansen's disease (*24*) and in the potential interactions with oncogenic viruses. Of some interest was the suggestion of a relationship of lymphoma risk with time since first use of dapsone, which may be related to the drug's capacity to cause lymphadenopathy (*25, 26*).

Although there were no significant increases in total cancer or lymphoma mortality, excess risks were observed for other sites, particularly of the urinary tract (bladder and kidney), oral cavity, and hepatobiliary system (liver and gallbladder).

The largest and most consistent excess was for urinary tract cancers, with the SMR for both bladder and kidney cancers being 3.2. There appeared to be no relationship with time since first admission or with first usage of sulfones, raising concern as to whether the association was spurious. It may be noteworthy, however, that an excess risk of bladder cancer has also been observed among renal transplant patients (*23*).

Excess risks were also observed for oral cancer. However, the tumors were quite heterogeneous, with 3 patients having cancers of the tongue and 1 each having cancers of the salivary gland, floor of the mouth, oropharynx, and hypopharynx. No information was available on smoking or alcohol use, which may have contributed to the risk of oral as well as esophageal cancers in this population (*27, 28*). However, the lack of a substantial excess risk of lung cancer would argue against smoking being an explanatory factor. Because of the many potential confounding influences coupled with the lack of a clear relationship with time since first admission, the reasons for the excess risk of upper alimentary tumors remain obscure. A high risk of these tumors with extended intervals since first exposure to sulfone therapy may warrant further attention, although in laboratory animals the neoplasms linked to dapsone were mesenchymal tumors of the spleen and peritoneum as well as thyroid tumors (*10–14*).

Some evidence also existed for a linear relationship of hepatobiliary cancers to length of exposure to sulfones. The finding was based on small numbers, and the risk rose only to a nonsignificant threefold excess for those initially exposed 10 years or more prior to death. However, the fact that 2 additional liver cancer deaths have subsequently occurred (5 and 19 mo after the end of follow-up) raises some concern, particularly since both patients had first been exposed to sulfones 20 years or more prior to death. Although we have no reason to believe that other factors may be responsible for the apparent sulfone-related excess of hepatobiliary cancer (e.g., history of hepatitis or alcoholic cirrhosis), more definitive interpretations will require further data collection, especially on sulfone exposure (since in our study primary consideration was given to medications prescribed during Carville admissions). In addition, the excess risk of hepatobiliary cancer in patients with lepromatous leprosy seems consistent with reports that the underlying immune defect may increase susceptibility to hepatitis B virus (*29*), a putative cause of liver cancer.

In summary, this follow-up study did not reveal a substantially increased cancer risk among patients with Hansen's disease. The risk of lymphoma also was not significantly increased among patients with lepromatous disease, despite immunologic perturbations that might be expected to predispose to lymphoma. There were certain other cancer sites (oral, bladder, and kidney) with elevated risks, although probably related to various confounding factors in this population.

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